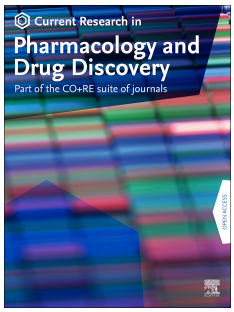
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



Physiopathology and prospectives for therapeutic treatment of pulmonary fibrotic state in COVID-19 patients

Antonio Vitiello, Francesco Ferrara

PII: S2590-2571(21)00043-2

DOI: https://doi.org/10.1016/j.crphar.2021.100056

Reference: CRPHAR 100056

To appear in: *Current Research in Pharmacology and Drug Discovery*

Received Date: 13 May 2021

Revised Date: 12 August 2021

Accepted Date: 9 September 2021

Please cite this article as: Vitiello, A., Ferrara, F., Physiopathology and prospectives for therapeutic treatment of pulmonary fibrotic state in COVID-19 patients, *Current Research in Pharmacology and Drug Discovery* (2021), doi: https://doi.org/10.1016/j.crphar.2021.100056.

Physiopathology and prospectives for therapeutic treatment of pulmonary fibrotic state in COVID-19 patients

Antonio Vitiello - Francesco Ferrara

Francesco Ferrara: Hospital Pharmacist Manager, Pharmaceutical department, Asl Napoli 3 Sud, Dell'amicizia street 22, 80035, Nola, Naples, Italy. https://orcid.org/0000-0001-9298-6783. Mail ferrarafr@libero.it. Tel and Fax:+390813223622.

Antonio Vitiello: Clinical Pharmacologist, Pharmaceutical department, Usl Umbria 1, A.Migliorati street, 06132, Perugia, Italy. https://orcid.org/0000-0003-2623-166X. Mail antonio.vitiello2@uslumbria1.it. Tel and Fax:+390755412609.

***author correspondence:** ferrarafr@libero.it

Abstract

The COVID-19 global pandemic has caused about 4,30 Mln deaths. Recently the first vaccines have been licensed, representing the most powerful weapon available to stop the pandemic. The COVID-19 viral infection in the most severe cases can cause severe lung lesions with the presence of fibrotic tissue. Even among cured individuals, the presence of pulmonary fibrotic tissue may be the major cause of long-term complications of COVID-19 requiring antifibrotic therapeutic treatment even in the post-COVID-19 infection phase to accelerate the healing process and fully recover lung function. This article reviews the fibrogenic mechanism of SARS-CoV-2-induced viral damage and the antifibrotic treatments indicated to treat sequelae post COVID-19 infection.

Keywords: Fibrotic, Pulmunary, Covid-19, Pharmacology, Pneumonia

Background

In November 2019, a sudden surge of patients admitted to hospitals in Wuhan, China, due to severe pneumonia of viral origin was identified[1]. The rapid exponential increase in the number of cases suggested the possibility of human-to-human transmission.[2-3] On January 7, 2020, Chinese scientists isolated a new coronavirus from samples taken from the airways of hospitalized patients[4]. This viral agent has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[5]. The World Health Organization (WHO) declared this new viral disease a global public health emergency on January 30, 2020, and subsequently declared SARS-CoV-2 global pandemic status (COVID-19) on March 11, 2020[6]. To date, data record 400 Mln infected and 4,30 Mln deaths worldwide. SARS-CoV-2, following spike (S) protein binding, penetrates host cells via attachment to the angiotensin-converting enzyme-2 (ACE2) receptor. After endocytosis, the viral RNA genome is released into the host cell. ACE-2 is expressed in numerous tissues; therefore, it is believed that SARS-CoV-2 can penetrate and infect several target organs, from the lungs to the heart, liver, and testes[7]. Transmission occurs from human to human[8]. The onset of the first symptoms of the disease has been reported within a period of 14 days after exposure to the virus. Current epidemiologic evidence indicates that the highest morbidity affects individuals of advanced age and with preexisting comorbidities. Because of the urgency and rapidity of action, treatments used to treat infection have been experimental and mostly indicated to avoid serious complications[9-10]. Recently, the first vaccines have been licensed, using mRNA, viral vector and protein subunit methods[11-12-13]. Pulmonary fibrosis caused by SARS-CoV-2 is an important clinical consequence of COVID-19 infection. Pulmonary fibrosis is also a common sequela of COVID-19 patients in recovery, compromising quality of life in some cases. Evidence has shown that cytokines involved in the development of pulmonary fibrosis are increased in severe COVID-19 patients, this suggests that pulmonary fibrosis plays an important role in the development of severe disease in COVID-19 patients.

SARS-CoV-2 and Pulmonary Fibrosis

Evidence shows that COVID-19 viral infection can exacerbate preexisting respiratory diseases, particularly pulmonary fibrose (PF). A direct pathophysiologic relationship between COVID-19 viral infection and stable or progressive fibrosis is not entirely clear, although some data suggest a potential fibrosis caused by the infection, even after recovery from the virus. [14-15] Fibrosis may take a course as a stable disease in response to infection, or progressive also characterized by periods of rapid exacerbation. COVID-19 can cause lung lesions with the presence of fibrotic tissue even after virus eradication. The fibrotic lung condition may be associated with a thickening of the alveolar walls obstructing the normal physiology of gas exchange and decreasing lung function. COVID-19 patients with symptomatic and then cured disease are at increased risk of developing fibrotic disease and long-term damage.[16] Therefore, it is critical to know the pathophysiological pathways activated by COVID-19 to identify the most effective targeted treatments to accelerate resolution and the healing process.[17-18-19] Although to date, the genetic predisposition that makes some individuals more susceptible to severe COVID-19 infection than others is still unclear, in view of the very high number of infected individuals, the best therapeutic strategies to treat the current infection, but also the post-infection sequelae, must be identified.

Pathophysiology of pulmonary fibrotic/inflammatory state by SARS-CoV-2

Bilateral interstitial pneumonia caused by COVID-19 infection is associated with the presence of fibrotic tissue caused by excess collagen (fibrosis) in the pulmonary interstitium with hyperinflammation present. SARS-CoV-2 infection in its most severe stages is characterized by a generalized hyperinflammatory state, induced by a cytokine storm, causing pulmonary and multi-organ injury. This massive and sudden release of proinflammatory cytokines, such as tumor necrosis factor alpha TNF-α and interleukin-1-beta (IL-1β) causes acute inflammatory fibrotic lung disease. At this stage of infection COVID-19, activated macrophages contribute to the induction of neutrophil recruitment[20] contributing to the generation of reactive oxygen species (ROS). This response is useful in eliminating the virus, but in excess and abnormal can result in tissue damage[21-22]. In addition, activation of fibroblasts deposits collagen to repair tissue damage. However, even when the fibroblast response is unregulated it can cause increased thickness, stiffness, and alteration of the normal structure of the lung pathways. Some evidence shows that the formation of fibrotic lung tissue in severe COVID-19 patient is also caused by an excess of chemokines[23]. Moreover, activated macrophages and fibroblasts produce large amounts of TGFb which produces increased extracellular matrix, collagen deposition, and subsequent increase in tissue stiffness. From a molecular point of view, other mechanisms are responsible for the formation of pulmonary fibrotic tissue in COVID-19 patients. In particular, SARS-CoV-2 penetrates cells through the ACE-2 receptor, this is expressed in alveolar pneumocytes. ACE2 is a regulator of the renin-angiotensin system (RAS). The RAS system consists of a classical ACE-dependent pathway and a nonclassical ACE-2-dependent pathway. In severe stages of COVID-19 infection, a dysregulated RAS system may contribute to excessive production of Ang II, synthesized by the classical ACE-dependent pathway, with profibrotic, and inflammatory effects. In contrast, the non-classical ACE-2 pathway appears to be reduced, with decreased production of antifibrotic and anti-inflammatory mediators such as Ang (1-7) and Ang (1-9).[24-25-26] Increased Ang II causes activation of tumor necrosis factor-a (TNFa), interleukin (IL)-6, TGFb, and increased recruitment of neutrophils and macrophages, which are critical factors in a fibrotic response. However, the increase in these described proinflammatory factors, increased Ang II, and activation of downstream mediated pathways should be carefully considered and evaluated even after recovery from COVID-19. *(Figure 1)*

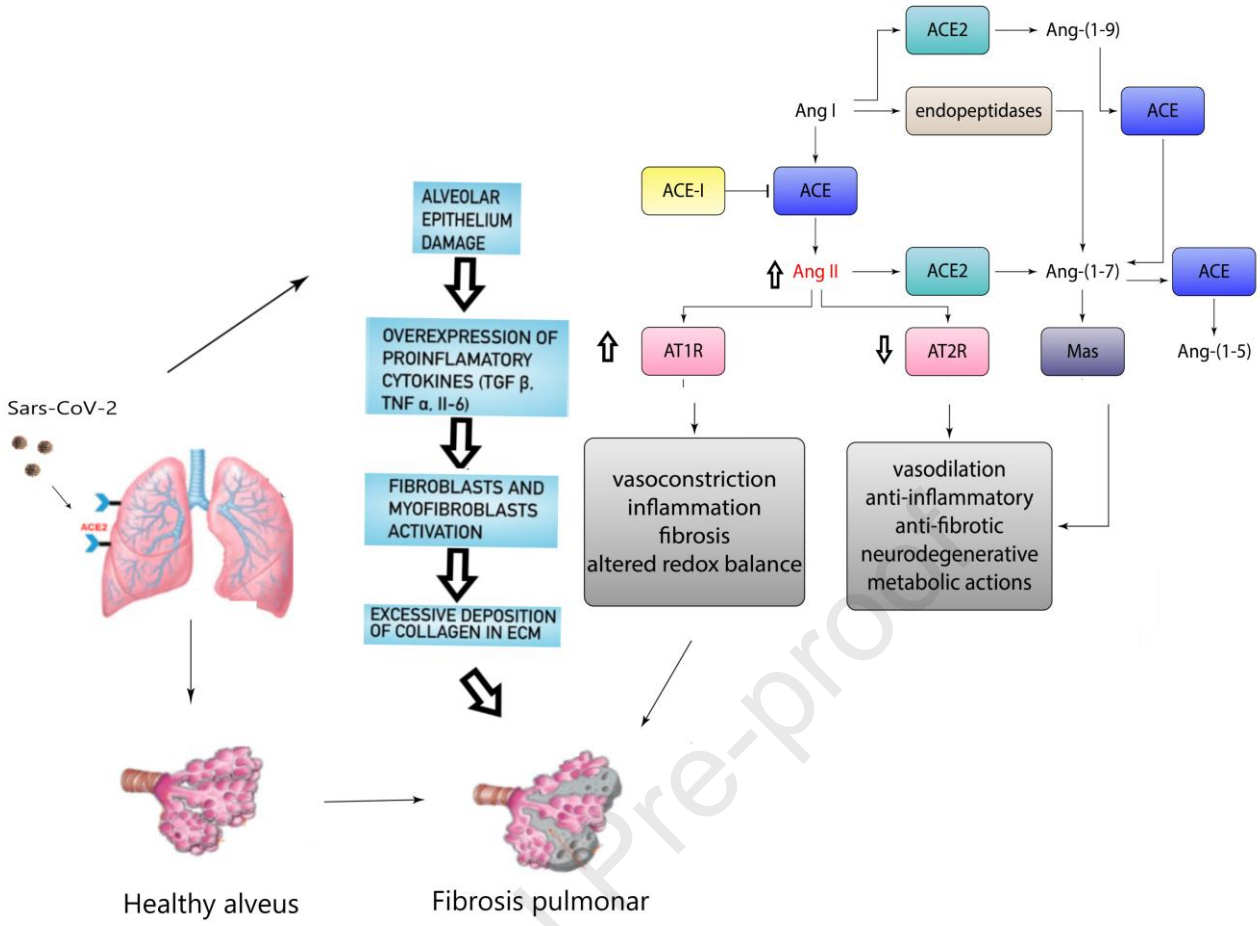


Figure 1: *Schematic representation of fibrotic tissue caused by COVID-19 infection and RAS system disregulation: SARS-CoV-2 penetrates lung cells via ACE-2. In the most severe stages of infection the hyperactive inflammatory state, recruitment and activation of macrophages, fibroblasts and neutrophils, decrease of ACE-2 and overproduction of Ang II cause inflammation, deposition of extracellular matrix, formation of fibrotic tissue.*

In the most severe phases of the infection, a generalized inflammatory state induced by the cytokinetic cascade may appear, and in parallel a state of systemic hypercoagulability characterized by the tendency of venous, arterial and microvascular thrombosis. In these subjects high levels of D-dimer and fibrinogen alterations, a slight prolongation of the prothrombin time are frequently detected. The consequent damage to the alveolar epithelium causes the release of pro-inflammatory cytokines and excessive deposition of collagen, with the formation of fibrotic tissue *(Figure 1)*. Several studies also show ARDS in the lungs and microangiopathic, hemorrhagic and thrombotic phenomena with widespread alveolar damage.

The direct viral damage at the endothelial level is determinant in the hyperactivation of coagulation.[27] The damage to the endothelium can cause circulatory dysfunction, vasoconstriction, with consequent ischemia and inflammation of the microcirculation. In addition, the inflammatory state itself is an important trigger for the coagulation cascade. Finally, the platelet component of coagulation is also activated during COVID-19 infection. In autopsy lung tissue, the abundant presence of megakaryocytes suggests a correlation with the finding of widespread small platelet-rich thrombi. Platelets, in fact, can promote an immune-mediated response causing tissue infiltration and, in critical phases, thrombocytopenia. The latter is essentially always present in severe pictures of COVID-19

disease.[28-29] This shows that the mechanism of pulmonary fibrosis in COVID-19 is different from that in IPF and other fibrotic lung diseases.

Risk Factors of pulmonary fibrotic/inflammatory state by SARS-CoV-2

Some evidence shows that certain risk factors such as age, severity of COVID-19 disease, use of mechanical ventilation, and smoking may contribute more to the development of pulmonary fibrosis.[30] Elderly patients are more likely to develop severe symptoms from COVID-19. Laboratory evidence indicates that elevated lactate dehydrogenase (LDH) levels correlate with increased disease severity and risk of developing pulmonary fibrosis. LDH is an indicator of lung tissue destruction and correlates with mortality risk. Severe COVID-19 patients may require intensive care. Mechanical ventilation may be an additional risk factor for ventilator-induced lung injury (VILI). Ventilator-induced lung injury is an acute lung injury resulting from or exacerbated by mechanical ventilation that leads to the release of proinflammatory mediators, presence of pulmonary fibrosis, and increased mortality. In a follow-up study of 27 patients undergoing mechanical ventilation for ARDS, 110-267 days after extubation, 23 patients (85%) had pulmonary fibrosis with a significant relationship to duration of ventilation.[30]

Pulmonary fibrotic state post COVID-19 infection

To date, there is open debate whether individuals recovered from COVID-19 infection with sequelae, may present with irreversible airway damage with the presence of progressive post-infection fibrose or reversible damage that with appropriate therapy may recur. Other outbreaks caused by similar viruses such as MERS or SARS-CoV suggest that post-infection pulmonary fibrose could be a problem. Epidemiologic evidence indicates that 33% of patients recovered from MERS had pulmonary fibrose in the postinfection setting[27]. Studies of SARS-CoV have indicated that 27.8% to 62% of patients infected with SARS-CoV showed decreased lung function and increased fibrose[31-32-33]. In a 15-year follow-up from the 2003 SARS outbreak, 9% of study participants experienced fibrose after infection, and this percentage decreased within 1 year and remained stable until a 15-year follow-up in 2018[34]. The study found that most patients recovered from interstitial damage and functional decline within 2 years of rehabilitation . What proportion of COVID- 19 patients developed pulmonary fibrose remains speculative and should not be assumed without an appropriate prospective study. A study shows[35] Lung lesions in 64.7% of discharged patients were completely absorbed after 4 weeks of follow-up. This indicated that lung damage caused by COVID-19 might be reversible for common COVID-19 patients. It also suggested that the prognosis of non-severe patients is favorable, and clinical intervention should be conducted in time to prevent common COVID-19 patients from worsening into severe patients. Many studies have shown that the most common abnormality of lung function in survivors discharged with COVID-19 is impaired diffusion capacity, followed by restrictive ventilatory defects, both of which are associated with disease severity[36-37]. The cytokine storm that occurs in the most severe stages of infection can lead to the initiation and promotion of pulmonary fibrosis. Dysregulated release of matrix metalloproteinases, VEGF, and cytokines cause epithelial and endothelial damage in the airways. In particular, some individuals develop progressive pulmonary fibrosis induced by the accumulation of fibroblasts excessive collagen deposition.

Molecular Biomarkers

Pulmonary fibrosis has been identified as the major cause of lung dysfunction in patients who survived severe SARS-CoV-2 infection. Thus, there is an urgent need to identify biomarkers for early detection of post COVID-19 infection patients at risk of developing persistent lung fibrosis with subsequent risk of mortality. Probably the data and knowledge acquired on the pathophysiological mechanisms of lung fibrosis can also be used to identify post-COVID-19 patients at higher risk of

persistent fibrotic lung damage by directing the best choices of drug treatment. A number of noninvasive, serologic biomarkers may be important to rapidly detect tissue remodeling and fibrosis, and subsequent decline in lung function[38] . In the absence of pathology, the extracellular matrix (ECM) in the airways separates capillaries from the alveolar space and allows gas diffusion. In the presence of fibrotic tissue, the ECM expands limiting this function. The fibrotic ECM is composed of fibronectin and collagen types I, III, and VI.[39] An important tool to prevent COVID-19 development of pulmonary fibrotic tissue is to understand the effects of COVID-19 infection on pulmonary ECM romodeling using appropriate markers. Neoepitope technology is useful to detect the generation of newly formed epitopes of collagens and other ECM proteins that form during fibrosis[40-41]. These neoepitope markers may be associated with the progression of Pulmonary Fibrosis in COVID-19 patients. The value of D-Dimer may also be considered, in severe COVID-19 patients there is dysregulation of coagulation.

A study stratified a sample of 239 patients with pulmonary fibrosis during hospitalization according to their degree of pulmonary fibrosis at discharge, biological marher and their clinical characteristics were analyzed. Patients with and without pulmonary fibrosis had statistically significant differences in age, IL-6 levels, % lymphocytes, aspartate transaminase (AST), albumin, CRP/albumin ratio, and platelet/lymphocyte ratio, suggesting that these abnormal clinical indicators may be related to pulmonary fibrosis.[42]

Antifibrotic treatment post COVID-19 infection needs to be undertaken in a timely manner in order to accelerate the healing process and resume full lung function

Pharmacological treatment of COVID-19 pulmonary fibrosis

The management of drug treatments of the severe COVID-19 patient is complex. The benefit/risk ratio of the pharmacologic agents used should be carefully monitored[43-44-45]. Appropriate use of medications may reduce the risk of severe COVID-19 complications and postinfection sequelae. To date, no fully proven epidemiological evidence is available for the treatment of post COVID 19 infection pulmonary fibrose, in this direction various treatment strategies are being evaluated. It has been proposed that the appropriate use of antivirals, antifibrotics[46-47-48], and anti-inflammatory agents reduces the risk of developing pulmonary fibrose. However, among the antivirals and anti-inflammatory drugs, it is yet to be fully elucidated which of them has the greatest efficacy in preventing lung remodeling and fibrosis. Synthetic glucocorticoid drugs and interleukin inhibitors (eg, Tocilizumab, Sarilumab) used in severe phases of COVID-19 infection, by reducing the hyperactive and generalized inflammatory state may indirectly also prevent the formation of fibrotic lung tissue[49]. Same rationale for use also applies to colchicine. The use of large doses of glucocorticoid drugs could worsen hyperglycemia and contribute to proximal myopathy, which in turn would delay patients' mobility and rehabilitation.[50]Pirfenidone and nintedanib, are drugs used for the treatment of Idiopathic Pulmonary Fibrosis (IPF).[51-52-53] They are drugs with pleiotropic, antifibrotic, antioxidant, and anti-inflammatory effects that can be used in the acute phase of COVID-19 infection and in the pharmacological treatment of the post COVID-19 pulmonary fibrotic state, for a better and faster healing process.[54-55-56] In particular, pirfenidone possesses anti-inflammatory activity by suppressing the activation of the NLRP3 inflammasome. Probably the use of pirfenidone immediately at the onset of acute respiratory syndrome from SARS-CoV-2 may prevent more consequences such as pulmonary fibrosis. In addition, it should be considered that both of these antifibrotic drugs require at least 1-3 months to demonstrate a clinical efficacy effect. This has been demonstrated in the INBUILD, and INPULSIS studies,[57-58] Thus, the time of initiation of antifibrotic treatment is critical; adding them at a late stage in patients requiring ventilatory support may not be optimal. Patients with the most severe ARDS are best suited for antifibrotic therapy. Such patients will generally require prolonged ventilation with high oxygen requirements, and perhaps antifibrotics along with steroids (which have already become the standard of care) could play a role in preventing or delaying the fibrosis that many of these patients will develop. Another interesting line of research to prevent and reduce the pulmonary fibrotic state in post COVID-19 infection patients is to act on

the RAS system. As described above, decreased expression of ACE-2 and increased synthesis of Ang II may result in inflammatory and profibrotic effects. Several agents under consideration could include soluble recombinant human ACE2 (hrsACE2) with a dual mechanism of action anti COVID-19, 2 binds the viral spike protein neutralizing SARS-CoV-2, and minimizes damage to multiple organs, including the lungs, kidneys, and heart, by reducing Ang II concentrations and increasing conversion to Ang (1-7) with anti-inflammatory antioxidant and antifibrotic effects. Another novel approach in this direction is the use of the ACE2-like enzyme[59-60-61]. An example of such experimental agents is B38-CAP. B38-CAP shares structural similarity with ACE2. In vitro evidence shows that the recombinant B38-CAP protein catalyzes the conversion of angiotensin II to Ang 1-7. Finally, another approach in this direction is the administration of Ang-derived plasma (1-7) in COVID-19-positive patients. Several clinical trials are underway to confirm these interesting hypotheses62[62-63-64]. Thus, the identification of biomarkers from the onset of COVID-19 infection is urgently needed to identify patients who are likely to progress to pulmonary fibrose. The use of anti-inflammatory and antibrotic therapy should be tailored with careful monitoring of the benefit/risk profile of the agents used. *(Figure 2)*

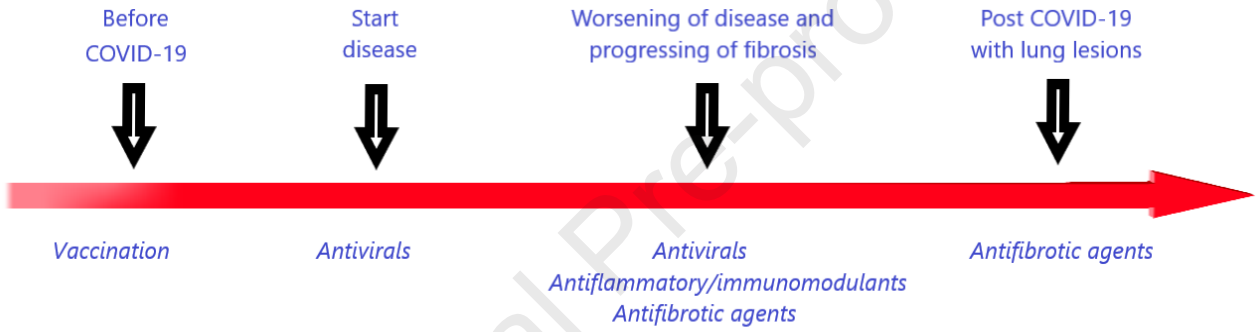


Figure 2: *Schematic view on timing of drug treatment to avoid/reduce pulmonary fibrotic tissue formation by COVID-19*

One of the most promising therapeutic approaches in the treatment of post COVID-19 pommel fibrosis is stem cell therapy(MSC)[65]. Infection with COVID-19 triggers an exaggerated exaggerated immune reaction in the body by producing large amounts of various inflammatory factors including several cytokines, chemokines, and immunoreactive cells. MSC therapy could prevent the triggering of the cytokine storm by the activated immune system, and the reparative properties of stem cells could promote endogenous repair. In addition, novel antifibrotic therapies may include molecules that block integrins and galectins in the TGF-beta pathway, and also act to inhibit viral infection.[66] Another treatment in Covid-19 are PDE4 inhibitors (PDE4i). These have recently been suggested as promising molecules to beat the severe inflammation in Covid-19 by acting to block the infiltration of neutrophils, monocytes, and lymphocytes and to reduce the production of inflammatory cytokines and chemokines from these cells and the lung epithelium.[67] Finally, those who have had significant respiratory disease may benefit from pulmonary rehabilitation.

CONCLUSIONS

Severe acute infection occurring in the airways of severe COVID-19 patients is a disease that can lead to pulmonary fibrosis and permanent disability.
There are few options available for its treatment. The most important factor in limiting pulmonary fibrosis is early, timely antiviral treatment and elimination of the causative viral agent, and anti-inflammatory treatment with glucocorticoids directed at reducing the inflammatory state that generates pulmonary fibrosis. In addition, antifibrotic therapies consisting of pirfenidone, nintedanib, and promising MSC therapy may be considered.In addition, another important line of research is the

use of molecules that act on the RAS system. Well-structured clinical trials are needed to generate additional and urgent evidence in this direction.

Conflicts of interest

None of the Authors have conflicts of interest to disclose.

Founds

None

Copyright

The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

Acknowledgement

The authors have nothing to say about ethical standards, ethical approval and funding. This manuscript is not a clinical trial and does not violate ethical rules. No funding has been received for its preparation.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470-473.

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020; 382: 1199-1207.

4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.

5. Islam KU, Iqbal J. An Update on Molecular Diagnostics for COVID-19. Front Cell Infect Microbiol. 2020;10:560616.

6. Guarner J. Three Emerging Coronaviruses in Two Decades. Am J Clin Pathol. 2020;153(4):420-421.

7. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.

8. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, Biology, and Structure-Based Therapeutics Development. Front Cell Infect Microbiol. 2020;10:587269.

9. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95.

10. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-810.

11. Vitiello A, Ferrara F, Pelliccia C, Granata G, La Porta R. Cytokine storm and colchicine potential role in fighting SARS-CoV-2 pneumonia. Italian Journal of Medicine. 2020;14(2), 88-94.

12. Vitiello A, Ferrara F. Pharmacological agents to therapeutic treatment of cardiac injury caused by Covid-19. Life Sci. 2020;262:118510.

13. Vitiello A, Ferrara F. Colchicine and SARS-CoV-2: Management of the hyperinflammatory state. Respir Med. 2021;178:106322.

14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062.

15. Naik PK, Moore BB. Viral infection and aging as cofactors for the development of pulmonary fibrosis. Expert Rev Respir Med. 2010;4(6):759-771.

16. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8(8):807-815.

17. Vitiello A, Ferrara F. Therapeutic Strategies for SARS-CoV-2 acting on ACE-2. Eur J Pharm Sci. 2021;156:105579.

18. Vitiello A, La Porta R, Ferrara F. Sacubitril, valsartan and SARS-CoV-2. BMJ Evid Based Med. 2020:bmjebm-2020-111497.

19. Vitiello A, Ferrara F. Remdesivir versus ritonavir/lopinavir in COVID-19 patients. Ir J Med Sci. 2020:1–2.

20. Ye C, Li H, Bao M, Zhuo R, Jiang G, Wang W. Alveolar macrophage - derived exosomes modulate severity and outcome of acute lung injury. Aging (Albany NY). 2020;12(7):6120-6128.

21. Deng Y, Herbert JA, Robinson E, Ren L, Smyth RL, Smith CM. Neutrophil-Airway Epithelial Interactions Result in Increased Epithelial Damage and Viral Clearance during Respiratory Syncytial Virus Infection. J Virol. 2020;94(13):e02161-19.

22. Herbert JA, Deng Y, Hardelid P, et al. β_2-integrin LFA1 mediates airway damage following neutrophil transepithelial migration during respiratory syncytial virus infection. Eur Respir J. 2020;56(2):1902216. Published 2020 Aug 6.

23. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, tenOever BR. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell. 2020;181(5):1036-1045.e9.

24. Vitiello A, Ferrara F. Correlation between renin-angiotensin system and Severe Acute Respiratory Syndrome Coronavirus 2 infection: What do we know? Eur J Pharmacol. 2020;883:173373.

25. Vitiello A, Pelliccia C, Ferrara F. Drugs acting on the renin-angiotensin system and SARS-CoV-2. Drug Discov Today. 2021 Jan 21:S1359-6446(21)00037-4.

26. Ferrara F, Vitiello A. Potential pharmacological approach in the regulation of ACE-2 and DPP-IV in diabetic COVID-19 patient. Italian Journal of Medicine. 2020.

27. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417-8.

28. Pick R, Begandt D, Stocker TJ, et al. Coronin 1A, a novel player in integrin biology, controls neutrophil trafficking in innate immunity. Blood 2017;130:847-58.

29. Moreau D, Timsit JF, Vesin A, et al. Platelet count decline: an early prognostic marker in critically ill patients with prolonged ICU stays. Chest 2007;131:1735-41.

30. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary fibrosis in COVID-19 survivors: Predictive factors and risk reduction strategies. Pulmonary Medicine. https:// doi.org/10.1155/2020/6175964.

31. Das KM, Lee EY, Singh R, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J Radiol Imaging. 2017;27(3):342-349.

32. Chan KS, Zheng JP, Mok YW, Li YM, Liu YN, Chu CM, Ip MS. SARS: prognosis, outcome and sequelae. Respirology. 2003;8 Suppl(Suppl 1):S36-40.

33. Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, Ko FW, Chan MC, Chan DP, Tong MW, Rainer TH, Ahuja AT, Cockram CS, Sung JJ. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax 2005;60:401-409.

34. Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, Ko FW, Chan MC, Chan DP, Tong MW, Rainer TH, Ahuja AT, Cockram CS, Sung JJ. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest. 2005;128(4), 2247–2261.

35. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, Chen L, Jiang M, Pan F, Zheng Y, Gao Z, Jiang B. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res 8,2020.

36. Liu C, Ye L, Xia R, Zheng X, Yuan C, Wang Z, Lin R, Shi D, Gao Y, Yao J, Sun Q, Wang X, Jin M. Chest Computed Tomography and Clinical Follow-Up of Discharged Patients with COVID-19 in Wenzhou City, Zhejiang, China. Ann Am Thorac Soc. 2020;17(10):1231-1237.

37. Nusair S. Abnormal carbon monoxide diffusion capacity in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;56(1):2001832.

38. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, Lei C, Chen R, Zhong N, Li S. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;55(6):2001217.

39. Leeming DJ, Genovese F, Sand JMB, Rasmussen DGK, Christiansen C, Jenkins G, Maher TM, Vestbo J, Karsdal MA. Can biomarkers of extracellular matrix remodelling and wound healing be used to identify high risk patients infected with SARS-CoV-2?: lessons learned from pulmonary fibrosis. Respir Res. 2021 Feb 5;22(1):38. doi: 10.1186/s12931-020-01590-y. PMID: 33546680; PMCID: PMC7863042.

40. Karsdal MA, et al. The good and the bad collagens of fibrosis— their role in signaling and organ function. Adv Drug Deliv Rev. 2017;121:43–56. 30.

41. Sand JMB, et al. High levels of biomarkers of collagen remodeling are associated with increased mortality in COPD—results from the ECLIPSE study. Respir Res. 2016;17:125. 31.

42. Karsdal MA, et al. Collagen biology and non-invasive biomarkers of liver fibrosis. Liver Int. 2020;40:736–50.

43. Zubairi ABS, Ahmad H, Hassan M, Sarwar S, Abbas A, Shahzad T, Irfan M. Clinical characteristics and factors associated with mortality in idiopathic pulmonary fibrosis: An experience from a tertiary care center in Pakistan. Clin Respir J. 2018 Mar;12(3):1191-1196. doi: 10.1111/crj.12650. Epub 2017 May 22. PMID: 28508572

44. Ferrara F. Antirheumatic in SARS-CoV-2: benefit or risk?. Italian Journal of Medicine. 2020; 14(2), 114-115. https://doi.org/10.4081/itjm.2020.1290.

45. Ferrara F, Porta R, Santilli P, D'Aiuto V, Vitiello A. Are multiple sclerosis therapies safe in severe acute respiratory syndrome coronavirus 2 times? Indian J Pharmacol. 2020;52(5):441-442.

46. Vitiello A, La Porta R, D'Aiuto V, Ferrara F. The risks of liver injury in COVID-19 patients and pharmacological management to reduce or prevent the damage induced. Egypt Liver Journal. 2020;11:11.

47. Vitiello A, Ferrara F, Porta R. Remdesivir and COVID-19 infection, therapeutic benefits or unnecessary risks? Ir J Med Sci. 2021:1–2.

48. Ferrara F, Porta R, D'Aiuto V, Vitiello A. Remdesivir and COVID-19. Ir J Med Sci. 2020:1–2.

49. Vitiello A, La Porta R, Ferrara F. Scientific hypothesis and rational pharmacological for the use of sacubitril/valsartan in cardiac damage caused by COVID-19. Med Hypotheses. 2021 Feb;147:110486.

50. Ferrara F, Vitiello A. Efficacy of synthetic glucocorticoids in COVID-19 endothelites. Naunyn Schmiedebergs Arch Pharmacol. 2021 Jan 14:1–5.

51. Vitiello A, La Porta R, D'Aiuto V, Ferrara F. Pharmacological approach for the reduction of inflammatory and prothrombotic hyperactive state in COVID-19 positive patients by acting on complement cascade. Hum Immunol. 2021:S0198-8859(21)00014-8.

52. Ferrara F, Granata G, Pelliccia C, La Porta R, Vitiello A. The added value of pirfenidone to fight inflammation and fibrotic state induced by SARS-CoV-2 : Anti-inflammatory and anti-fibrotic therapy could solve the lung complications of the infection?. Eur J Clin Pharmacol. 2020;76(11):1615-1618.

53. Vitiello A, Porta R, Pianesi L, Ferrara F. COVID-19 pandemic: vaccine and new monoclonal antibodies, point of view. Ir J Med Sci. 2021 Mar 12. doi: 10.1007/s11845-021-02584-5. Epub ahead of print. PMID: 33710481.

54. Ferrara F, Vitiello A. Scientific Hypothesis for Treatment of COVID-19's Lung Lesions by Adjusting ACE/ACE2 Imbalance. Cardiovasc Toxicol. 2021 Apr 9:1–6. doi: 10.1007/s12012-021-09649-y. Epub ahead of print. PMID: 33835386; PMCID: PMC8032553.

55. Vitiello A, Ferrara F. Pharmacological agents modifying the renin angiotensin and natriuretic peptide systems in COVID-19 patients. Wien Klin Wochenschr. 2021 Apr 20. doi: 10.1007/s00508-021-01855-6. Epub ahead of print. PMID: 33877436.

56. Vitiello A, Ferrara F. Anti-fibrotic therapy for the treatment of pulmonary sequelae in patients healed by COVID-19. Lung India. 2021 Mar;38(Supplement):S129-S130. doi: 10.4103/lungindia.lungindia_803_20. PMID: 33687000.

57. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, Moua T, Crestani B, Wuyts WA, Stowasser S, Quaresma M, Goeldner RG, Schlenker-Herceg R, Kolb M; INBUILD trial investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020 May;8(5):453-460. doi: 10.1016/S2213-2600(20)30036-9. Epub 2020 Mar 5. PMID: 32145830.

58. Crestani B, Huggins JT, Kaye M, Costabel U, Glaspole I, Ogura T, Song JW, Stansen W, Quaresma M, Stowasser S, Kreuter M. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. Lancet Respir Med. 2019 Jan;7(1):60-68. doi: 10.1016/S2213-2600(18)30339-4. Epub 2018 Sep 14. PMID: 30224318.

59. Ferrara, F., Vitiello, A. The advantages of drug treatment with statins in patients with SARS-CoV-2 infection. *Wien Klin Wochenschr* (2021). https://doi.org/10.1007/s00508-021-01845-8

60. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado Del Pozo C, Prosper F, Romero JP, Wirnsberger G, Zhang H, Slutsky AS, Conder R, Montserrat N, Mirazimi A, Penninger JM. Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. Cell. 2020;181(4):905-913.e7.

61. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875-9.

62. Haschke M, Schuster M, Poglitsch M, Loibner H, Salzberg M, Bruggisser M, Penninger J, Krähenbühl S. Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects. Clin Pharmacokinet. 2013;52(9):783-92.

63. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care. 2017;21(1):234.

64. Minato T, Nirasawa S, Sato T, Yamaguchi T, Hoshizaki M, Inagaki T, Nakahara K, Yoshihashi T, Ozawa R, Yokota S, Natsui M, Koyota S, Yoshiya T, Yoshizawa-Kumagaye K, Motoyama S, Gotoh T, Nakaoka Y,

Penninger JM, Watanabe H, Imai Y, Takahashi S, Kuba K. B38-CAP is a bacteria-derived ACE2-like enzyme that suppresses hypertension and cardiac dysfunction. Nat Commun. 2020;11(1):1058.

65. Li Z, Niu S, Guo B, Gao T, Wang L, Wang Y, Wang L, Tan Y, Wu J, Hao J. Stem cell therapy for COVID-19, ARDS and pulmonary fibrosis. Cell Prolif. 2020 Dec;53(12):e12939. doi: 10.1111/cpr.12939. Epub 2020 Oct 24. PMID: 33098357; PMCID: PMC7645923.

66. George P.M., Wells A.U., Jenkins R.G. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8(8):807–815.

67. Bridgewood C., Damiani G., Sharif K. Rationale for evaluating PDE4 inhibition for mitigating against severe inflammation in COVID-19 pneumonia and beyond. Isr. Med. Assoc. J. 2020;22:335–339.

Conflict of interest

I, The undersigned, Francesco Ferrara and any other author, declare that:

- The manuscript was written entirely by the authors;
- All authors made an equal contribution in the development of the paper;
- We have no conflict of interest;
- We have not received funding/source;
- There are no sensitive data and no patients were recruited for this study;
- The document does not conflict with ethical legislation.
- The authors accept the full TRANSFER OF COPYRIGHT to the journal.

Ethical Approval
Not applicable

Consent to Participate
Not applicable

Consent to Publish
The authors consent to the publication of the manuscript

Authors Contributions
AV: Conceptualization, Writing - original draft, Methodology, Writing - original draft.

FF: Writing - review & editing, Supervision, Validation.

All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used

Conflicts of interest
None of the Authors have conflicts of interest to disclose.

Founds
None

Availability of data and materials
Full availability of data and materials